An Efficient Procedure for the Preparation of 4-Methyl-2-thiocoumarins by the Reaction of 4-Methylcoumarins with Lawesson's Reagent

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Dedicated to Professor Dr. Lubor Fisera on the occasion of his 60th birthday

A simple and convenient method has been worked out for the preparation of 4-methyl-2-thiocoumarins by the reaction of the appropriate 4-methylcoumarins with Lawesson's Reagent in hot anhydrous toluene.

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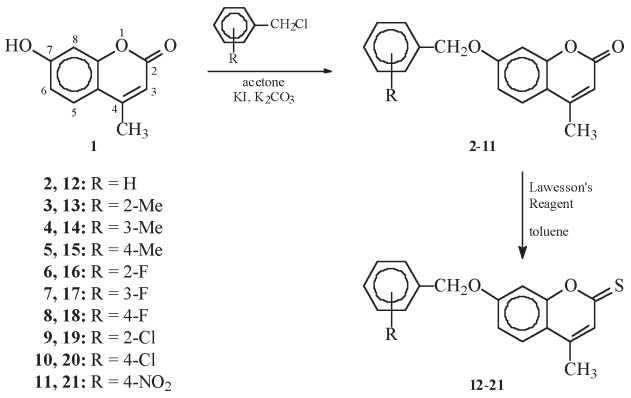
First synthesis of the 7-hydroxy-4-methylcoumarin (β-methylumbelliferone) (**1**) was performed by von Pechmann and Duisberg [1] as early as 1883 by the reaction of resorcinol and ethyl acetoacetate. Later, von Pechmann *et al*. [2,3] worked out other procedures for the synthesis of this coumarin. Drysdale *et al*. [4] reacted resorcinol and methyl 2,3-butadienoate to obtain 7-hydroxy-4-methylcoumarin (**1**). Another method, invented by Taylor and Cassell [5], is based on the reaction of 2,4-dihydroxyacetophenone and trimethylsilylketene and affords compound **1** in high (86%) yield. This hydroxycoumarin was successfully utilized as starting material for the synthesis of a wide variety of 4-methylcoumarin derivatives.

4-Methylcoumarin-7-yloxy tetra-*N*-acetyl-β-chitotetroside and similar β-chitotrioside were obtained under Koenigs-Knorr reaction conditions [6]. A neuraminic acid derivative has also been synthesized [7]. All these glycosides were utilized for enzyme inhibition studies [6,7].

Sulfate and sulfamate derivatives were synthesized for steroid sulfatase assay [8]. Various 7-alkoxy-4-methylcoumarins, including β-lactam [9], benzyloxy [10], phenazine [11] and carboxymethyl derivatives [12] were prepared by the reaction of the 7-hydroxy group of compound **1** with the appropriate reagent. Most of these coumarins were used for enzyme inhibition studies and other biological purposes. All these examples unequivocally prove the synthetic utility of the β-umbelliferone even today.

Various 7-benzyloxycoumarins have already been synthesized for enzyme inhibition studies [10]. On the basis of the results obtained with these compounds, it appeared expedient to synthesize a series of 7-benzyloxy-4-methylcoumarins systematically substituted in their benzyl moiety. Compound **1** was allowed to react with benzyl chlorides substituted either with an electron donor or an electron acceptor substituent in hot acetone solution to afford new 7-benzyloxy-4-methylcoumarins **3-11** in high (71-93%) yields (Scheme 1). The new coumarin derivatives can be advantageously utilized for the study of structure-activity relationships.

Scheme 1



2, 12: R = H
3, 13: R = 2-Me
4, 14: R = 3-Me
5, 15: R = 4-Me
6, 16: R = 2-F
7, 17: R = 3-F
8, 18: R = 4-F
9, 19: R = 2-Cl
10, 20: R = 4-Cl
11, 21: R = 4-NO_2

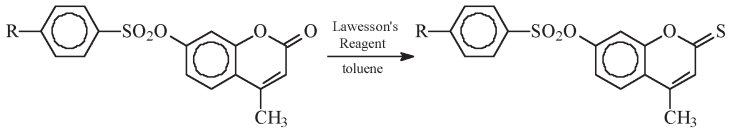
Although numerous 4-methylcoumarin derivatives have been synthesized, their conversion into 4-methyl-2-thiocoumarins has hitherto received less attention. 7-Methoxy-4-methyl-2-thiocoumarin was prepared by the reaction of 7-methoxy-4-methylcoumarin with silicon disulphide or boron sulphide [13] in refluxing chloroform and with phosphorus pentasulphide [14] in hot benzene. However, these reagents sometimes require special care which may be a disadvantage concerning their utilization. The consequence of this difficulty is that nowadays these reagents are almost out of use.

In our previous studies, Lawesson's Reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] [15] proved to be the reagent of choice for the replacement of an oxygen atom by a sulfur atom in the case of chromones [16], 1-thiochromones [17], flavones [18], isoflavones [16], 1,4- and 1,5-benzoxazepines [19-21] and 1,5-benzothiazepines [22]. Therefore, this reagent has been considered convenient for the conversion of 4-methylcoumarins into 4-methyl-2-thiocoumarins as well.

7-Benzyloxy-4-methylcoumarins **2-11** were allowed to react with Lawesson's Reagent [15] in hot anhydrous toluene and 7-benzyloxy-4-methyl-2-thiocoumarins **12-21** were obtained in high (75-91%) yields (Scheme 1).

7-Benzenesulfonyloxy-4-methylcoumarin (**22**) [23] and 4-methyl-7-tosyloxycoumarin (**23**) [23] have also been treated with Lawesson's Reagent under the same reaction conditions to afford the 2-thioanalogues **24** and **25** in high (89% and 90%) yields (Scheme 2).

Scheme 2



22: R = H
23: R = Me

24: R = H
25: R = Me

Structures of all new compounds (**3-11**, **12-21, 24** and **25**) have been elucidated by elemental analyses, mass spectrometry, ^{1}H and ^{13}C nmr spectroscopies (*cf.* Experimental). Both ^{1}H and ^{13}C nmr spectra unequivocally prove the structure of each compound. Formation of the 4-methyl-2-thiocoumarin derivatives is reflected in the downfield shift of the 3-H proton signal in their ^{1}H nmr spectra. In the ^{13}C nmr spcetra a C=S signal appears at around 197 ppm instead of the C=O signal at about 161 ppm.

Electron impact (70 eV) mass spectra of these coumarins are very similar and relatively simple. A molecular ion can be observed in all cases and the base peak is mainly the Ar(R)-CH_2^+ ion. Fragmentation of the coumarin ring system corroborates the structures elucidated by nmr spectroscopic measurements.

In summary, we have introduced a simple and convenient procedure for the preparation of 4-methyl-2-thiocoumarins. The Lawesson's Reagent could be advantageously utilized in the case of these coumarin derivatives for the replacement of an oxygen atom by a sulfur atom, too.

EXPERIMENTAL

Melting points were determined with a Koffler hot-stage apparatus and are uncorrected. Nmr spectra were recorded on the Varian 200 spectrometer at 200/50 MHz in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm) at room temperature. Mass spectra were measured on the VG TRIO-2 in the EI mode at 70 eV. Elemental analyses were measured in-house with a Carlo Erba 1106 EA apparatus. Tlc was performed on Kieselgel 60 F_{254} (Merck) layer using 1,2-dichloroethane or hexane:acetone (7:3 v/v) as eluents. Starting materials **1**, **2**, **22** and **23** were synthesized according to known procedures [10,23].

General Procedure for the Preparation of 7-Benzyloxy-4-methylcoumarins **3-11**.

A mixture of 7-hydroxy-4-methylcoumarin (**1**, 20.0 mmoles), appropriately substituted benzyl chloride (22.0 mmoles), potassium iodide (0.5 g), potassium carbonate (10.0 g) and anhydrous acetone (200 ml) was refluxed for 6 h, then the inorganic salts were removed by filtration. The solvent was evaporated under reduced pressure and the residue was crystallized from methanol to obtain compounds **3-11**.

4-Methyl-7-(2-methylbenzyloxy)coumarin (**3**).

This compound was prepared as white needles in 90% yield, mp 148-149°; ^{1}H nmr: δ 2.50 (3H, s, Me), 2.52 (3H, s, Me), 5.12 (2H, s, CH_2), 6.18 (1H, s, 3-H), 6.93-7.56 (m, 7 arom. H); ^{13}C nmr: δ 18.3, 18.6, 69.9, 101.8, 112.0, 112.8, 113.8, 125.6, 126.2, 128.7, 130.6, 133.7, 136.8, 152.6, 155.3, 161.3, 161.9; ms: 280 (M^+, 5), 176 (2), 147 (2), 105 (100) *m/z.*

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.26; H, 5.78.

4-Methyl-7-(3-methylbenzyloxy)coumarin (**4**).

This substance was obtained as white needles in 85% yield, mp 94-95°; ^{1}H nmr: δ 2.50 (3H, s, Me), 2.53 (3H, s, Me), 5.12 (2H, s, CH_2), 6.17 (1H, s, 3-H), 6.91-7.57 (m, 7 arom. H); ^{13}C nmr: δ 18.4, 21.2, 70.5, 101.2, 112.1, 112.9, 113.8, 124.7, 125.6, 128.3, 128.7, 129.2, 135.9, 138.9, 152.6, 155.4, 161.4, 161.9; ms: 280 (M^+,11), 176 (3), 147 (3), 105 (100) *m/z.*

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.29; H, 5.69.

4-Methyl-7-(4-methylbenzyloxy)coumarin (**5**).

This compound was isolated as white needles in 79% yield, mp 125-126°; ^{1}H nmr: δ 2.50 (3H, s, Me), 2.53 (3H, s, Me), 5.10 (2H, s, CH_2), 6.14 (1H, s, 3-H), 6.90-7.53 (m, 7 arom. H); ^{13}C nmr: δ 18.3, 20.9, 70.3, 101.9, 111.9, 112.9, 113.7, 125.6, 127.7, 129.5, 132.9, 138.3, 152.6, 155.3, 161.4, 161.9; ms: 280 (M^+, 4), 176 (2), 147 (2), 105 (100) *m/z.*

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.34; H, 5.72.

7-(2-Fluorobenzyloxy)-4-methylcoumarin (**6**).

This substance was prepared as white plates in 74% yield, mp 146-147°; ^{1}H nmr: δ 2.51 (3H, s, Me), 5.23 (2H, s, CH_2), 6.18 (1H, s, 3-H), 6.92-7.57 (m, 7 arom. H); ^{13}C nmr: δ 18.3, 64.1, 101.9, 112.1, 112.6, 113.9, 115.3, 115.7, 124.4, 125.7, 129.8, 130.3, 152.6, 155.3, 161.2, 161.6; ms: 284 (M^+, 8), 176 (2), 147 (2), 109 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}FO_3$: C, 71.82; H, 4.61. Found: C, 71.75; H, 4.66.

7-(3-Fluorobenzyloxy)-4-methylcoumarin (**7**).

This compound was obtained as white plates in 80% yield, mp 149-150°; ^{1}H nmr: δ 2.44 (3H, s, Me), 5.17 (2H, s, CH_2), 6.18

(1H, s, 3-H), 6.88-7.54 (m, 7 arom. H); ^{13}C nmr: δ 18.4, 69.5, 101.9, 112.2, 112.8, 114.0, 114.5, 115.0, 115.4, 122.8, 125.7, 130.5, 138.6, 152.6, 155.4, 161.3, 161.5; ms: 284 (M^+, 11), 176 (2), 147 (2), 109 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}FO_3$: C, 71.82; H, 4.61. Found: C, 71.78; H, 4.64.

7-(4-Fluorobenzyloxy)-4-methylcoumarin (**8**).

This substance was prepared as white plates in 87% yield, mp 134-135°; ^{1}H nmr: δ 2.44 (3H, s, Me), 5.11 (2H, s, CH_2), 6.16 (1H, s, 3-H), 6.89-756 (m, 7 arom. H); ^{13}C nmr: δ 18.4, 69.7, 101.9, 112.2, 112.8, 113.9, 115.5, 115.9, 125.7, 129.6, 131.7, 152.6, 155.4, 161.3, 161.7; ms: 284 (M^+, 5), 262 (1), 147 (3), 109 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}FO_3$: C.71.82; H, 4.61. Found: C, 71.89; H, 4.64.

7-(2-Chlorobenzyloxy)-4-methylcoumarin (**9**).

This substance was obtained as pale yellow needles in 93% yield, mp 154-155°; ^{1}H nmr: δ 2.41 (3H, s, Me), 5.26 (2H, s. CH_2), 6.17 (1H, s, 3-H), 6.90-7.53 (m, 7 arom. H); ^{13}C nmr: δ 18.4, 67.5, 102.2, 112.3, 112.7, 114.0, 125.7, 127.2, 128.9, 129.5, 129.7, 132.9, 133.7, 152.6, 155.4, 161.3, 161.6; ms: 300 (M^+, 8), 176 (2), 147 (2), 125 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36. Found: C, 67.98; H, 4.31.

7-(4-Chlorobenzyloxy)-4-methylcoumarin (**10**).

This compound was prepared as pale yellow plates in 88% yield, mp 139-140°; ^{1}H nmr: δ 2.42 (3H, s, Me), 5.12 (2H, s, CH_2), 6.17 (1H, s, 3-H), 6.88-7.52 (m, 7 arom. H); ^{13}C nmr: δ 18.3, 69.5, 101.9, 112.2, 112.8, 113.9, 125.7, 128.8, 128.9, 134.2, 134.5, 152.6, 155.3, 161.2, 161.6; ms: 300 (M^+, 6), 176 (2), 147 (4), 125 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}ClO_3$: C, 67.89; H, 4.36. Found: C, 67.98; H, 4.32.

4-Methyl-7-(4-nitrobenzyloxy)coumarin (**11**).

This substance was obtained as yellow needles in 71% yield, mp 204-205°; ^{1}H nmr: δ 2.44 (3H, s, Me), 5.24 (2H, s, CH_2), 6.18 (1H, s, 3-H), 6.87-8.30 (m, 7 arom. H); ^{13}C nmr: δ 18.0, 68.6, 101.9, 111.6, 112.8, 113.7, 123.8, 126.8, 128.6, 144.4, 147.4, 153.6, 154.9, 160.3, 161.2; ms: 311 (M^+, 10), 176 (2), 147 (2), 136 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}NO_5$: C, 65.59; H, 4.21; N, 4.49. Found: C, 65.48; H, 4.25; N, 4.43.

General Procedure for the Preparation of 4-Methyl-2-thiocoumarins **12-21, 24** and **25**.

A mixture of 4-methylcoumarin (**2-11**, **22** and **23**, 5.0 mmoles), Lawesson's Reagent (6.0 mmoles) and anhydrous toluene (30 ml) was refluxed for 3 h and then the solvent was evaporated under reduced pressure. The residue was crystallized from methanol to afford 4-methyl-2-thiocoumarins **12-21**, **24** and **25**.

7-Benzyloxy-4-methyl-2-thiocoumarin (**12**).

This compound was obtained as yellow needles in 77% yield, mp 151-152°; ^{1}H nmr: δ 2.32 (3H, s, Me), 5.14 (2H, s. CH_2), 6.97-7.58 (m, 3-H + 8 arom. H); ^{13}C nmr: δ 17.7, 70.5, 101.5, 114.7, 115.5, 125.6, 126.7, 127.5, 128.5, 128.9, 135.7, 144.9, 158.0, 162.2, 197.6; ms: 282 (M^+, 17), 250 (3), 136 (3), 91 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{14}O_2S$: C, 72.33; H, 4.99. Found: C, 72.46; H, 4.92.

4-Methyl-7-(2-methylbenzyloxy)-2-thiocoumarin (**13**).

This compound was isolated as yellow needles in 89% yield, mp 148-149°; ^{1}H nmr: δ 2.35 (3H, s, Me), 2.40 (3H, s, Me), 5.12 (2H, s, CH_2), 6.96-7.60 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.8, 18.6, 69.2, 101.7, 114.7, 115.5, 125.6, 126.3, 126.7, 128.6, 128.8, 130.7, 133.5, 136.7, 145.0, 158.1, 162.4, 197.6; ms: 296 (M^+, 11), 218 (10), 155 (8), 105 (100) *m/z*.

Anal. Calcd. for $C_{18}H_{16}O_2S$: C, 72.96; H, 5.44. Found: C, 72.982; H, 5.49.

4-Methyl-7-(3-methylbenzyloxy)-2-thiocoumarin (**14**).

This substance was obtained as yellow needles in 76% yield, mp 127-128°; ^{1}H nmr: δ 2.31 (3H, s, Me), 2.38 (3H, s, Me), 5.08 (2H, s, CH_2), 6.97-7.56 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.8, 21.2, 70.6, 101.4, 114.8, 115.5, 124.6, 125.6, 126.7, 128.3, 128.8, 129.3, 135.6, 138.6, 145.0, 158.0, 162.3, 197.6; ms: 296 (M^+, 19), 264 (3), 155 (6), 105 (100) *m/z*.

Anal. Calcd. for $C_{18}H_{16}O_2S$: C, 72.96; H, 5.44. Found: C, 73.11; H, 5.37.

4-Methyl-7-(4-methylbenzyloxy)-2-thiocoumarin (**15**).

This compound was prepared as yellow needles in 75% yield, mp 164-165°; ^{1}H nmr: δ 2.32 (3H, s, Me), 2.38 (3H, s, Me), 5.10 (2H, s, CH_2), 6.97-7.56 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.7, 20.9, 70.4, 101.4, 114.7, 115.3, 125.5, 126.6, 127.6, 129.5, 132.6, 138.3, 145.0, 157.9, 162.3, 197.5; ms: 296 (M^+, 16), 264 (2), 147 (3), 105 (100) *m/z*.

Anal. Calcd. for $C_{18}H_{16}O_2S$: C, 72.96; H, 5.44. Found: C, 72.84; H, 5.48.

7-(2-Fluorobenzyloxy)-4-methyl-2-thiocoumarin (**16**).

This substance was obtained as yellow plates in 91% yield, mp 201-202°; ^{1}H nmr: δ 2.37 (3H, s, Me), 5.11 (2H, s, CH_2), 6.97-7.60 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.8, 64.4, 101.5, 114.6, 115.5, 115.9, 124.5, 125.7, 126.9, 129.8, 130.4, 130.6, 144.9, 158.0, 162.0, 197.6; ms: 300 (M^+, 22), 268 (3), 147 (2), 109 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}FO_2S$: C, 67.99; H, 4.36. Found: C, 67.85; H, 4.31.

7-(3-Fluorobenzyloxy)-4-methyl-2-thiocoumarin (**17**).

This compound was prepared as yellow plates in 75% yield, mp 147-148°; ^{1}H nmr: δ 2.34 (3H, s, Me), 5.14 (2H, s, CH_2), 6.96-7.58 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.7, 69.6, 101.4, 114.0, 115.1, 115.7, 122.8, 125.7, 126.8, 130.6, 138.3, 144.9, 157.9, 161.9, 165.6, 197.5; ms: 300 (M^+, 19), 268 (4), 147 (2), 109 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}FO_2S$: C, 67.99; H, 4.36. Found: C, 68.12; H, 4.29.

7-(4-Fluorobenzyloxy)-4-methyl-2-thiocoumarin (**18**).

This compound was obtained as yellow needles in 82% yield, mp 135-136°; ^{1}H nmr: δ 2.36 (3H, s, Me), 5.10 (2H, s, CH_2), 6.96-7.60 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.7, 69.8, 101.4, 114.7, 115.6, 116.0, 125.7, 126.8, 129.4, 129.6, 131.4, 144.9, 158.0, 160.4, 162.0, 165.4, 197.6; ms: 300 (M^+, 13), 268 (2), 147 (2), 109 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}FO_2S$: C, 67.99; H, 4.36. Found: C, 67.81; H, 4.27.

7-(2-Chlorobenzyloxy)-4-methyl-2-thiocoumarin (**19**).

This substance was prepared as yellow plates in 88% yield, mp 171-172°; ^{1}H nmr: δ 2.36 (3H, s, Me), 5.26 (2H, s, CH_2), 7.03-762 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.8, 67.7, 101.6, 114.5, 115.7, 125.7, 126.9, 128.8, 129.6, 132.9, 133.4, 144.9, 158.0, 161.9, 197.6; ms: 316 (M^+, 15), 284 (2), 147 (2), 125 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}ClO_2S$: C, 64.46; H, 4.14. Found: 64.38; H, 4.19.

7-(4-Chlorobenzyloxy)-4-methyl-2-thiocoumarin (**20**).

This compound was obtained as yellow plates in 82% yield, mp 155-156°; ^{1}H nmr: δ 2.34 (3H, s, Me), 5.12 (2H, s, CH_2), 6.97-7-59 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.8, 69.7, 101.5, 114.6, 115.6, 125.7, 126.9, 128.9, 129.0, 134.2, 134.4, 144.9, 157.9, 161.9, 197.5; ms: 316 (M^+, 12), 284 (2), 147 (2), 125 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}ClO_2S$: C, 64.46; H, 4.14. Found: C, 64.53; H, 4.21.

4-Methyl-7-(4-nitrobenzyloxy)-2-thiocoumarin (**21**).

This compound was prepared as yellow plates in 76% yield, mp 198-199°; ^{1}H nmr: δ 2.32 (3H, s, Me), 5.25 (2H, s, CH_2), 6.98-8.26 (m, 3-H + 7 arom. H); ^{13}C nmr: δ 17.7, 69.1, 101.5, 114.1, 115.9, 124.0, 125.9, 127.0, 127.8, 143.1, 144.7, 147.9, 157.9, 161.5, 197.5; ms: 327 (M^+, 60), 281 (11), 192 (43), 148 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{13}NO_4S$: C, 62.38; H, 4.01; N, 4.28. Found: C, 62.51; H, 4.08; N, 4.21.

7-Benzenesulfonyloxy-4-methyl-2-thiocoumarin (**24**).

This substance was obtained as yellow needles in 89% yield, mp 177-178°; ^{1}H nmr: δ 2.34 (3H, s, Me), 7.03-7.90 (m, 3-H + 8 arom. H). ^{13}C nmr: δ 17.7, 55.4, 95.0, 96.2, 110.6, 119.7, 125.8, 128.4, 129.2, 129.6, 134.9, 143.2, 151.7, 156.3, 197.0; ms: 332 (M^+, 57), 191 (24), 141 (46), 77 (100) *m/z*.

Anal. Calcd. for $C_{16}H_{12}O_4S_2$: C, 57.83; H, 3.64. Found: 57.95; H, 3.56.

4-Methyl-7-tosyloxy-2-thiocoumarin (**25**).

This compound was prepared as yellow needles in 90% yield, mp 140-141° ; ^{1}H nmr: δ 2.l9 (3H, s, Me), 2.26 (3H, s, Me), 7.04-7.80 (m, 3-H + 7 arom. H), ^{13}C nmr: δ 17.7, 21.6, 120.0, 120.4, 125.7, 128.5, 129.2, 130.2, 143.2, 146.3, 151.9, 156.4, 197.2; ms: 346 (M^+, 27), 314 (4), 155 (46), 91 (100) *m/z*.

Anal. Calcd. for $C_{17}H_{14}O_4S_2$: C, 58.96; H, 4.07. Found: C, 58.84; H, 4.13.

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